

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 4 : A61K 33/24, 31/29	A1	(11) International Publication Number: WO 89/ 03219 (43) International Publication Date: 20 April 1989 (20.04.89)
(21) International Application Number: PCT/AU88/00379 (22) International Filing Date: 29 September 1988 (29.09.88) (31) Priority Application Numbers: PI 4838 PI 5985 PI 7513 (32) Priority Dates: 12 October 1987 (12.10.87) 18 December 1987 (18.12.87) 30 March 1988 (30.03.88) (33) Priority Country: AU (71)(72) Applicant and Inventor: BORODY, Thomas, Julius [AU/AU]; 144 Great North Road, Five Dock, NSW 2046 (AU). (74) Agent: SPRUSON & FERGUSON; G.P.O. Box 3898, Sydney, NSW 2001 (AU).		(81) Designated States: AT (European patent), AU, BE (European patent), CH (European patent), DE (European patent), FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent), US. Published <i>With international search report.</i>
(54) Title: IMPROVED METHOD FOR TREATMENT OF GASTROINTESTINAL DISORDERS (57) Abstract <p>The present invention provides a method for eradicating and/or preventing recurrence of gastrointestinal disorders associated with <i>Campylobacter pylori</i> infections, which involves the administration of a pharmaceutical composition, comprising a pharmaceutically acceptable bismuth compound with a first antibiotic and a second antibiotic. There is also provided a pharmaceutical composition for the treatment of gastrointestinal disorders associated with <i>C. pylori</i>, and pharmaceutical compositions for said treatment in the form of a sequential pack.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	ML	Mali
AU	Australia	GA	Gabon	MR	Mauritania
BB	Barbados	GB	United Kingdom	MW	Malawi
BE	Belgium	HU	Hungary	NL	Netherlands
BG	Bulgaria	IT	Italy	NO	Norway
BJ	Benin	JP	Japan	RO	Romania
BR	Brazil	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	LI	Liechtenstein	SN	Senegal
CH	Switzerland	LK	Sri Lanka	SU	Soviet Union
CM	Cameroon	LU	Luxembourg	TD	Chad
DE	Germany, Federal Republic of	MC	Monaco	TG	Togo
DK	Denmark	MG	Madagascar	US	United States of America
FI	Finland				

- 1 -

IMPROVED METHOD FOR TREATMENT OF GASTRO INTESTINAL DISORDERSTECHNICAL FIELD

This invention relates to pharmaceutical compositions and therapeutic methods for eradication and/or prevention of recurrence of gastrointestinal disorders associated with infection by Campylobacter Pylori

BACKGROUND ART

C. pylori is a recently described bacterium found to cause chronic histological gastritis. Its causal role in peptic ulceration is less clear and even less so in non-ulcer dyspepsia. Its role could be more effectively studied if effective therapy for its eradication were devised.

Until recent times, C. pylori has been found to be difficult to eradicate using known chemotherapeutic agents. Although many antibiotics can suppress C. pylori growth in vitro, in vivo the mucosal concentration appears to be inadequate and penetration of the usual gastric mucus layer poor. Hence, development of an adequate in vivo eradication method for chronic C. pylori infection has been difficult. Moreover, adequate prediction of in vivo results cannot be predicted from in vitro work.

European Patent Application No. 206,625 and Australian Patent Application No. 59026/86 describe the use of bismuth together with a single antibiotic for the treatment of C. pylori. However, bismuth alone achieves low (30 to 70%) initial clearance rates for C. pylori and recurrence of the infection approaches 100% by twelve months post therapy. Bismuth together with a single antibiotic, namely amoxicillin, appears to be relatively effective as a short term means of reducing the symptoms but it is now clear that the use of bismuth together with a single antibiotic frequently fails to eradicate the infection and has a high rate of infection recurrence (Rauws, Erik A. J. et al; Gastro-enterology, 1988; 94: 33-40).

DISCLOSURE OF THE INVENTION

The present inventor has now found that the use of a multi antibiotic therapy not only results in a high initial clearance rate of C. pylori, of the order of greater than 90%, but also leads to a high eradication rate where most patients remain free of infection for more than twelve to eighteen months. It now seems that therapeutic success measured at eight weeks biopsy (post treatment) should be termed as clearance only whilst the term "eradication" should be used in the context of patients who remain free of C. pylori infection for more than twelve months post treatment.

FJF/821f

- 2 -

The present inventor has also found that C. pylori is not only associated with gastritis but is also causally associated with peptic ulcer including duodenal, pre-pyloric, gastric, oesophageal and marginal ulcer and consequently the novel therapy for eradication of C. pylori described in the present invention is useful in the treatment of peptic ulcer as well as non-ulcer dyspepsia. Moreover, the novel therapy of the present invention is useful in the treatment of oesophageal reflux, reflux oesophagitis as well as asymptomatic carrier states.

In one broad form the present invention provides a pharmaceutical composition for the treatment of gastro intestinal disorders associated with C. pylori infections comprising a pharmaceutically acceptable bismuth compound, a first antibiotic or antimicrobial agent and a second antibiotic or antimicrobial agent.

In a further form the invention provides a sequential pack comprising a first pharmaceutical composition in unit dosage form adapted and presented in said pack for a first administration period of 3 to 36 days, said first composition comprising a pharmaceutically acceptable bismuth compound and a first antibiotic or antimicrobial agent together with a second pharmaceutical composition comprising a second antibiotic or antimicrobial agent in unit dosage form adapted and presented in said pack for a second administration period different from said first administration period.

The invention also provides a sequential pack for the administration of at least two pharmaceutical compositions comprising a first composition which comprises a pharmaceutically acceptable bismuth compound, a first antibiotic or antimicrobial agent and a second antibiotic or antimicrobial agent, in unit dosage form adapted and presented for a first administration period of 3 to 36 days, together with a second pharmaceutical composition which comprises an acid suppressant for ulcer treatment in unit dosage form adapted and presented for a second administration period of 3 to 36 days prior to or overlapping with the initial part of said first administration period.

Preferably, the first antibiotic or antimicrobial agent is selected from one or more of tetracyclines, penicillins, quinolones, cephalosporins, furazolidones, lincosamides, nitrofurantoin and/or polypeptides. Preferably, the second antibiotic or antimicrobial agent is selected from one or more of quinolones, furazolidones, nitrofurantoin, metronidazoles, and/or cephalosporins.

More preferably the first antibiotic or antimicrobial agent is
FJF/821f

- 3 -

selected from tetracyclines and/or penicillins and the second antibiotic is a metronidazole.

The tetracyclines include tetracycline, oxytetracycline, doxycycline, demeclocycline, methacycline and minocycline.

The penicillins include penicillin G, penicillin V, oxacillin, nafcillin, ampicillin, amoxicillin, cloxacillin and carbenicillin.

The metronidazoles include metronidazole and tinidazole.

Rifampin, trimethoprim and/or nalidixic acid may also be used.

The cephalosporins include cephalexin (Keflex), cefaclor, cephradine, cephradine and cefadroxil as well as second and third generation cephalosporins.

The polypeptide antibiotics include polymyxin B, bacitracin, colistin sulfate and/or spectinomycin HCl.

Quinolones include ciprofloxacin, norfloxacin and ofloxacin.

Lincosamides include lincomycin and clindamycin.

Whilst it is preferred that the first and second antibiotics or antimicrobial agents are selected from different classes, they may be selected from within the one class. Moreover, a third or more antibiotics may be included in the methodology and compositions of the invention; eg amoxicillin, tetracycline and metronidazole. Keflex is also preferably used as one of the first or second antibiotics or as a further antibiotic.

Bismuth compounds suitable in the present invention include those selected from the group consisting of bismuth aluminate, bismuth subcarbonate, bismuth subcitrate, bismuth citrate, tripotassium dicitrate bismuthate, bismuth subgalate, bismuth subnitrate, bismuth tartrate, bismuth salicylate, bismuth subsalicylate, and mixtures thereof. Bismuth citrate, bismuth subcitrate, tripotassium dicitrate bismuthate, bismuth tartrate, bismuth subsalicylate, and mixtures thereof are preferred bismuth salts for use in this invention. The bismuth useful herein may be administered alone, or in combination with other pharmaceutically-acceptable components, in a bismuth-containing composition. A variety of such compositions containing bismuth salts are commercially-available, including, for example, DeNol, containing tripotassium dicitrate bismuthate (sold by Gist-Brocades N.V.), Noralac, containing bismuth aluminate, alginic acid, and magnesium carbonate (manufactured by North American Pharmaceuticals), Roter bismuth, containing bismuth subnitrate (sold by Roter Laboratories), Fensobar Polvo, containing bismuth subcarbonate among other materials (manufactured by USV Pharmaceutical Corporation), and Pepto-Bismol, containing bismuth subsalicylate (sold by The Procter & FJF/821f

- 4 -

Gamble Company)).

In a preferred form of the present invention there is provided a method of treating gastro intestinal infections associated with C. pylori which comprises administering an effective amount of a pharmaceutically acceptable bismuth compound in combination with a tetracycline and/or a penicillin and a metronidazole.

In a further aspect of the present invention there is provided a capsule for oral administration to patients suffering from gastro intestinal infections associated with C. pylori wherein said capsule includes a pharmaceutically acceptable bismuth compound together with a first antibiotic and a second antibiotic wherein said capsule is adapted to release said bismuth within the stomach of the recipient and wherein at least said first antibiotic and preferably also said second antibiotic is microencapsulated so that said first and optionally said second antibiotic is released within the gastro intestinal tract after said stomach.

In a preferred form of this aspect of the invention there is provided a capsule containing an effective amount of a pharmaceutically acceptable bismuth compound together with enteric coated micro-spherules of an antibiotic of the tetracycline class or penicillin class which capsule also contains an effective amount of a second antibiotic selected from the metronidazole class which second antibiotic is optionally provided in enteric coated micro-spherule form.

In a further aspect of the present invention the methodology uses the treatment regimen comprising the combination of pharmaceutically acceptable bismuth compound in combination with a first antibiotic and a second antibiotic for between three to twenty-eight days. Preferably the treatment is combined with the administration of an acid suppressant such as an histamine₂ antagonist such as cimetidine, ranitidine or famotidine to effect symptomatic relief and ulcer epithelialization. This is followed by the combination of the bismuth and first and second antibiotic therapy. Preferably the histamine₂ antagonist is administered for three to twenty-eight days followed by a three to twenty-eight day therapy of the bismuth/antibiotics combination. Other acid suppressants may be used instead of an histamine₂ antagonist such as benzimidazole or prostoglandins. Alternatively, the histamine₂ blocker or other acid suppressant can be combined with the pharmaceutical composition of the present invention.

The present invention also provides a sequence presented pack suitable for therapy for gastro intestinal disorders associated with C.
FJF/821f

- 5 -

pylori infection which combines a pharmaceutically acceptable bismuth compound together with a first antibiotic and a second antibiotic and optionally further antibiotics so that said treatment regimen can be adapted for individual patient needs. Optionally the sequence presented pack may also include an initial therapy comprising an acid suppressant such as a histamine₂ antagonist or a K/Na ATP-ase inhibitor such as omeprazole and may be combined with mucus disrupting agents such as carbocysteine, n-acetylcysteine, corticosteroids or bisolvon. It should be noted that the pharmaceutical composition comprises at least two antibiotics but further antibiotics may be selectively added in difficult cases or where resistant strains and/or multiple strains present a more resistant problem.

In the composition and methodology of the present invention, preferably from 5 to 5000mg, more preferably 50 to 250mg of a pharmaceutically acceptable bismuth compound is used together with from 5 to 10000mg, more preferably 50 to 500mg of a first antibiotic together with from 5 to 10000mg, more preferably 50 to 250mg of a second antibiotic.

Preferably the invention provides a pharmaceutical composition containing from 50 to 250mg of a colloidal bismuth in pharmaceutically acceptable form, 50 to 500mg of tetracycline or a penicillin (eg amoxicillin) type antibiotic and 50 to 250mg of a metronidazole type antibiotic such as metronidazole or tinidazole. Preferably the tetracycline or penicillin is microencapsulated to prevent bismuth chelation at high pH.

In a further aspect the invention provides a sequential pack comprising an antimicrobial pharmaceutical composition in unit dosage form adapted for an administration period of three to thirty-six days, said antimicrobial composition comprising a pharmaceutically acceptable bismuth compound, at least a first antibiotic and at least a second antibiotic, together with a palliative pharmaceutical composition in unit dosage form adapted and presented for a three to thirty-six day administration period prior to, or overlapping with the initial part of the administration period of said antimicrobial pharmaceutical composition wherein said palliative pharmaceutical composition comprises a therapeutic agent such as an acid suppressant, adapted for ulcer treatments.

In a further aspect the invention provides a sequential pack comprising a first pharmaceutical composition in unit dosage form adapted for an administration period of three to thirty six days, said composition comprising a pharmaceutically acceptable bismuth compound and at least a

FJF/821f

- 6 -

first antibiotic, together with a second pharmaceutical composition in unit dosage form comprising a second antibiotic adapted for administration for a period different to said administration period of said first pharmaceutical composition. Preferably the pack further comprises a palliative pharmaceutical composition in unit dosage form presented in said pack in a 3 to 36 day administration period which is prior to or overlaps with the initial part of the administration period of said first pharmaceutical composition wherein said palliative pharmaceutical composition comprises a therapeutic agent, such as an acid suppressant, adapted for ulcer treatment.

BEST MODES OF CARRYING OUT THE INVENTION

The methodology and treatment described above is useful in the treatment of disorders associated with C. pylori which include duodenal ulcer, pre-pyloric ulcer, gastric ulcer, oesophageal ulceration, reflux oesophagitis with or without ulceration, bile-reflux "gastritis" non ulcer dyspepsia associated with C. pylori gastritis and/or asymptomatic carrier state.

Whilst tablets or capsules of the pharmaceutical composition of the present invention are preferred, sachets or syrups or other orally ingestible forms of the compositions are also included within the scope of the present invention.

The invention will be further described with reference to the following test procedure of the Example and accompanying Figures wherein Figure 1 shows the results of treatment of the present invention in 64 out of 100 patients at an average of 19.3 months post treatment and Figure 2 shows the histologic grading pre and post treatment with the treatment of the present invention.

EXAMPLE

Test Procedure

Patients aged 19 to 79 years (M:F = 47:53) with symptoms of dyspepsia lasting three months or more referred for endoscopy, were entered. Only patients positive for C. pylori with either duodenal ulcer or non-ulcer dyspepsia were entered into the study. Patients were deemed to have non-ulcer dyspepsia if, in the absence of ulcer or other disease, they complained of food related epigastric discomfort or pain, bloating, belching, nausea, a feeling of fullness or heartburn. Patients with duodenal ulcer were entered into the treatment protocol only after ulcer treatment with either four weeks of ranitidine (300mg/day) or cimetidine

FJF/821f

- 7 -

(800mg/day), known not to influence C. pylori. Exclusion criteria included coagulopathy, antibiotic use within two weeks of endoscopy, presence of oesophageal varices, previous gastrectomy, neoplasm, systemic disease or allergy preventing use of the medications. Gastric ulcer patients were excluded to form a separate study. Of 122 patients entered in the study, 112 completed the triple chemotherapy adequately. Of these, 100 consecutive re-endoscoped patients became available for analysis of results at eight weeks after commencement of treatment and constitutes the short term follow up group. Ten patients did not complete the treatment due to failure to follow up (4), nausea (2), clostridium difficile-positive diarrhoea (1), allergy (2), and oral moniliasis (1). At 12 to 37 months after C. pylori eradication therapy CP-negative patients at eight weeks from the pilot studies and the abovementioned group were invited for re-examination by gastroscopy. Of the entire cohort 64 patients returned for examination and constitute the long term follow up group.

Gastroscopy

All examinations were carried out by the same endoscopist. Two biopsy specimens were taken from the gastric antrum and one from the body. One antral specimen was placed in a microtitre tray containing buffered urea and an indicator to detect rapidly presence of C. pylori urease activity. The other specimens were placed in 10% buffered formalin for histological examination. No bacterial cultures were carried out.

Histological Assessment

Paraffin sections of tissues fixed in formalin were stained with haematoxylin and eosin to grade severity of histological gastritis and with Warthin-Starry silver stain to grade C. pylori density. Grading was based on density of lymphocyte/plasma cell (chronic), neutrophil (active) infiltration, or presence of C. pylori from 0 to III as previously described.

Specimens were graded by the same consultant histopathologist without knowledge of patients' details.

Medication

Except for eight patients allergic to tetracycline, all subjects received a combination of colloid bismuth substrate (108mg chew-tablets q.i.d.), tetracycline HCl (500mg q.i.d.) for four weeks, together with metronidazole (200mg q.i.d.) for the first ten days. Amoxicillin (500mg

FJF/821f

- 8 -

q.i.d.) was substituted for tetracycline in the eight allergic patients. Patients and endoscopist were not blinded to the treatment regimen. Patients were asked if they had completed the medication as requested but no tablet count was attempted.

Assessment of Symptoms

For patients with idiopathic non-ulcer dyspepsia (NUD) a questionnaire form was developed and administered six months following clearance of C. pylori. Global assessment of percent improvement in these patients is reported below. In duodenal ulcer patients symptom improvement or disappearance was recorded.

RESULTS

Clearance of C. Pylori at eight weeks

Of the 100 consecutive available patients treated for C. pylori, 94 were negative on urease testing and histology at eight weeks after commencement of chemotherapy (See Table 1). The six patients remaining positive at eight weeks claimed to have taken their medication as directed.

Long Term Clearance of C. pylori

Follow up gastroscopic biopsies were obtained in 64 patients (M:F = 36:28) at 12 to 37 months after original triple chemotherapy (mean = 19.3 months), and results shown in Fig. 1. These patients were drawn from the 94 who remained CP negative at eight weeks post therapy and from a small pilot study carried out some months earlier. Of these 64, paid recalled volunteers who resubmitted to gastroscopic biopsy, 33 had been originally diagnosed as having non-ulcer dyspepsia while 28 had endoscopically-proven duodenal ulcer. At follow up overall 60 or 94% remained free of C. pylori infection at the 19.3 months. One of the 33 NUD patients was again positive for the bacteria while three of 31 patients originally with duodenal ulcer were CP positive. In the latter three patients, two again had re-ulcerated while the other patient had pronounced duodenitis. All 28 patients who remained free of C. pylori maintained their ulcers endoscopically healed. They were on no maintenance therapy and were free of ulcer-like symptoms.

In NUD patients, as a global assessment in the 32 cleared patients, 25/32 (78%) reported a "50% or more improvement" over their initial symptom scores. On the other hand in four other patients with NUD in spite of CP eradication and reversal of histologic gastritis no improvement in

FJF/821f

- 9 -

dyspeptic symptoms occurred.

An unexpected finding in four of 15 patients who initially had linear oesophageal ulceration, was total healing and disappearance of the ulcers after C. pylori eradication. No appreciable weight change had occurred in these patients and the improvement could not be ascribed to any other medical therapy.

Table 1

Patient	Age	M/F	<u>C. pylori</u> at start of treatment	<u>C. pylori</u> 8wks past therapy
1 N.U.D	65	F	+ve	-ve
2 D.U	59	M	+ve	-ve
3 N.U.D	62	F	+ve	-ve
4 N.U.D	63	M	+ve	-ve
5 N.U.D	35	M	+ve	-ve
6 P.P.U	74	F	+ve	-ve
7 G.U 3	40	F	+ve	+ve*
8 D.U	65	M	+ve	-ve
9 2 D.U	55	F	+ve	-ve
10 D.U	60	M	+ve	+ve*
11 N.U.D	60	M	+ve	-ve
12 N.U.D	66	M	+ve	-ve
13 P.P.U	59	M	+ve	-ve
14 N.U.D	28	F	+ve	-ve
15 P.P.U	36	M	+ve	-ve
16 D.U	22	M	+ve	-ve
17 D.U	42	F	+ve	-ve
18 N.U.D	65	F	+ve	-ve
19 D.U	32	M	+ve	-ve
20 D.U	65	M	+ve	-ve
21 N.U.D	61	M	+ve	-ve
22 D.U	29	F	+ve	+ve*
23 N.U.D	29	M	+ve	-ve
24 N.U.D	30	M	+ve	-ve
25 D.U	74	M	+ve	-ve
26 N.U.D	42	M	+ve	-ve
27 N.U.D	38	M	+ve	+ve*
28 P.P.U	51	F	+ve	-ve
29 N.U.D	26	M	+ve	-ve

- 10 -

Table 1 cont'd

Patient		Age	M/F	<u>C. pylori</u> at start of treatment	<u>C. pylori</u> 8wks past therapy
30	D.U	44	F	+ve	-ve
31	D.U	50	M	+ve	-ve
32	N.U.D	29	F	+ve	-ve
33	N.U.D	72	F	+ve	-ve
34	N.U.D	29	M	+ve	-ve
35	N.U.D	22	F	+ve	-ve
36	D.U	28	M	+ve	-ve
37	D.U	54	M	+ve	-ve
38	N.U.D	44	F	+ve	-ve
39	N.U.D	56	F	+ve	-ve
40	N.U.D	40	M	+ve	-ve
41	N.U.D		M	+ve	-ve
42	N.U.D	65	F	+ve	-ve
43	G.U/D.U	53	F	+ve	-ve
44	N.U.D	43	M	+ve	-ve
45	N.U.D	73	F	+ve	-ve
46	N.U.D		F	+ve	-ve
47	N.U.D	46	F	+ve	-ve
48	N.U.D	41	M	+ve	-ve
49	N.U.D	46	F	+ve	-ve
50	N.U.D	34	M	+ve	-ve
51	N.U.D	58	F	+ve	-ve
52	N.U.D	51	F	+ve	-ve
53	N.U.D	23	M	+ve	-ve
54	N.U.D	54	F	+ve	-ve
55	D.U	59	F	+ve	-ve
56	P.P.U	31	M	+ve	-ve
57	O.U	56	M	+ve	-ve
58	N.U.D	33	M	+ve	-ve
59	PREV G.U	78	M	+ve	-ve
60	N.U.D	63	M	+ve	-ve
61	N.U.D	27	M	+ve	-ve
62	N.U.D	45	F	+ve	-ve
63	N.U.D	38	M	+ve	-ve
64	N.U.D	36	M	+ve	-ve

- 11 -

Table 1 cont'd

Patient	Age	M/F	<u>C. pylori</u> at start	<u>C. pylori</u> 8wks
			of treatment	past therapy
65 N.U.D	66	F	+ve	-ve
66 N.U.D	70	F	+ve	-ve
67 P.P.U	66	F	+ve	-ve
68 D.U	37	F	+ve	-ve
69 N.U.D	64	M	+ve	-ve
70 N.U.D	45	M	+ve	-ve
71 N.U.D	24	F	+ve	-ve
72 N.U.D	46	M	+ve	-ve
73 N.U.D	53	F	+ve	-ve
74 N.U.D	33	M	+ve	-ve
75 N.U.D	30	M	+ve	-ve
76 N.U.D	42	F	+ve	-ve
77 D.U	36	M	+ve	-ve
78 N.U.D	64	F	+ve	-ve
79 D.U	34	M	+ve	-ve
80 N.U.D	65	F	+ve	-ve
81 N.U.D	56	M	+ve	+ve*
82 N.U.D	42	M	+ve	-ve
83 N.U.D	43	F	+ve	-ve
84 N.U.D	75	F	+ve	-ve
85 N.U.D	62	F	+ve	-ve
86 N.U.D	64	F	+ve	-ve
87 N.U.D	51	M	+ve	-ve
88 N.U.D	39	M	+ve	-ve
89 N.U.D	39	F	+ve	-ve
90 N.U.D	40	M	+ve	-ve
91 N.U.D	34	F	+ve	-ve
92 N.U.D	60	M	+ve	-ve
93 N.U.D	59	M	+ve	-ve
94 N.U.D	67	M	+ve	-ve
95 N.U.D	60	F	+ve	-ve
96 N.U.D	38	M	+ve	-ve
97 N.U.D	53	M	+ve	+ve*
98 N.U.D	51	M	+ve	-ve
99 N.U.D	54	M	+ve	-ve

- 12 -

Table 1 cont'd

Patient	Age	M/F	<u>C. pylori</u> at start of treatment	<u>C. pylori</u> 8wks past therapy
100 N.U.D	56	M	+ve	-ve

* indicates failure to cure infection.

D.U = Duodenal ulcer

O.U = Oesophageal ulcer

P.P.U = Pre-pyloric ulcer

G.U = Gastric ulcer

N.U.D = Non-ulcer dyspepsia

Histological Changes

The effects of therapy on histological grading of C. pylori density as well as lymphocyte and neutrophil infiltration are summarized in Figure 2.

Histological scores have been arbitrarily assigned to show graphically the time-course of inflammation resolution. All patients presented initially with high scores for both chronic and active gastritis. Neutrophil infiltration disappeared rapidly paralleling C. pylori clearance. Lymphocyte infiltration, on the other hand, persisted for a much longer time.

This study has demonstrated that high (> 90%) initial "clearance" of gastric C. pylori is possible with a combination of available antimicrobial agents. Such a high level of initial clearance has not been previously achieved. It is also clear that therapeutic success measured at the eight week biopsy, should for the present be termed "clearance". The term "eradication" should be reserved for patients remaining free of CP beyond six months. In this study most of those patients cleared of CP at eight weeks remained clear of the infection for more than twelve months.

Although C. pylori is susceptible to numerous antibiotics in vitro, such agents notoriously fail to eradicate it in vivo. Bismuth appears to be an important component in the combination chemotherapy. While it is not clear why several antimicrobials are required to improve eradication of CP, antibiotic access to the bacteria may be a problem. The bismuth compound may be required locally within the gastric pits and mucus whereas the antibiotics could be required to be carried systemically to reach bacteria deep in gastric pits and within endocytotic vacuoles. Presence of multiple strains of C. pylori with varying antibiotic susceptibility spectra could provide another explanation for the need to employ multiple antibiotics.

FJF/821f

- 13 -

In view of the multiplicity of strains, it is in fact surprising that such a high CP clearance rate could be achieved employing only two systemic antimicrobials and one locally-acting agent (CBS). Perhaps the success can be further explained by prevention of the development of resistant strains seen after short courses of single systemic antibiotics.

A clinically useful method for successful long term C. pylori eradication has not previously been described. Twelve month follow up figures of 51% and 35% have been reported using bismuth plus a single antibiotic. Such therapy would clearly be unsatisfactory for patients and may lead to creation of resistant C. pylori strains. It is also desirable to have an effective eradication therapy for C. pylori before embarking upon a double-blind trial designed to demonstrate the relevance of the organism in a particular disease.

Although it is known that bismuth can decrease tetracycline bioavailability, the antibiotic combination as used here achieved its desired effect in spite of presumed chelation. It would appear that adequate bismuth and tetracycline remained post-chelation to reach the infected targets. It is known also that chelation is in part pH dependent and low pH protects against chelation. As some patients with C. pylori infection will have impaired gastric acid secretion, elevated pH may have contributed to treatment failures. Other sources of treatment failure could include reduction in tetracycline bioavailability by ingestion of milk, antacids, iron or food, or simply non-compliance.

- 14 -

CLAIMS

1. A pharmaceutical composition for the treatment of gastro intestinal disorders associated with Campylobacter pylori infections comprising a pharmaceutically acceptable bismuth compound, a first antibiotic or antimicrobial agent and a second antibiotic or antimicrobial agent.
2. The composition of Claim 1, wherein said bismuth compound is selected from the group consisting of bismuth aluminate, bismuth subcarbonate, bismuth subcitrate, colloidal bismuth subcitrate, bismuth citrate, tripotassium dicitrate bismuthate, bismuth subgalate, bismuth subnitrate, bismuth tartrate, bismuth subsalicylate, bismuth salicylate, bismuth subsalicylate, and mixtures thereof.
3. The composition of Claim 1 or claim 2, wherein said first antibiotic or antimicrobial agent is selected from one or more of tetracyclines, penicillins, quinolones, cephalosporins, furazolidones, lincosamides, nitrofurantoin, and/or polypeptides.
4. The composition of any one of Claims 1 to 3, wherein said second antibiotic or antimicrobial agent is selected from one or more of quinolones, furazolidones, metronidazoles, and/or cephalosporins.
5. The composition of Claim 1, wherein said first antibiotic or antimicrobial agent is a penicillin or tetracycline.
6. The composition of Claim 1, wherein said second antibiotic or antimicrobial agent is a metronidazole.
7. The composition of Claim 5, wherein said penicillin or tetracycline is microencapsulated.
8. The composition of any one of Claims 1 to 7, further comprising a third antibiotic or antimicrobial agent.
9. A sequential pack comprising a first pharmaceutical composition in unit dosage form adapted and presented in said pack for a first administration period of 3 to 36 days, said first composition comprising a pharmaceutically acceptable bismuth compound and a first antibiotic or antimicrobial agent together with a second pharmaceutical composition comprising a second antibiotic or antimicrobial agent in unit dosage form adapted and presented in said pack for a second administration period different from said first administration period.
10. The sequential pack of Claim 9, further comprising a palliative pharmaceutical composition in unit dosage form presented in said pack for a third administration period of 3 to 36 days prior to or overlapping with

- 15 -

the initial part of said first administration period, wherein said palliative pharmaceutical composition comprises an acid suppressant adapted for ulcer treatment.

11. A sequential pack for the administration of at least two pharmaceutical compositions comprising a first composition which comprises a pharmaceutically acceptable bismuth compound, a first antibiotic or antimicrobial agent and a second antibiotic or antimicrobial agent, in unit dosage form adapted and presented for a first administration period of 3 to 36 days, together with a second pharmaceutical composition which comprises an acid suppressant for ulcer treatment in unit dosage form adapted and presented for a second administration period of 3 to 36 days prior to or overlapping with the initial part of said first administration period.

12. The sequential pack of any one of Claims 9 to 11, wherein said bismuth compound is selected from the group consisting of bismuth aluminate, bismuth subcarbonate, bismuth subcitrate, colloidal bismuth subcitrate, bismuth citrate, tripotassium dicitritobismuthate, bismuth subgalate, bismuth subnitrate, bismuth tartrate, bismuth salicylate, bismuth subsalicylate and mixtures thereof.

13. The sequential pack of any one of Claims 9 to 12, wherein said first antibiotic or antimicrobial agent is selected from one or more of tetracyclines, penicillins, quinolones, cephalosporins, furazolidones, lincosamides, nitrofurantoin and/or polypeptides.

14. The sequential pack of any one of Claims 9 to 13, wherein said second antibiotic or antimicrobial agent is selected from one or more of quinolones, furazolidones, nitrofurantoin, metronidazole, and/or cephalosporins.

15. The sequential pack of Claim 13, wherein said first antibiotic or antimicrobial agent is a penicillin or tetracycline.

16. The sequential pack of Claim 14, wherein said second antibiotic or antimicrobial agent is a metronidazole.

17. The sequential pack of Claim 15, wherein said penicillin or tetracycline is microencapsulated.

18. The sequential pack of any one of Claims 10 to 17, wherein said acid suppressant is a histamine₂ antagonist or K/Na ATP-ase inhibitor.

19. A method for the eradication and/or prevention of recurrence of gastrointestinal disorders associated with C. pylori infections in a patient requiring said eradication and/or prevention, which method comprises administering an effective amount of a composition of any one of claims 1 to 8.

FJF/821f

- 16 -

20. The method of Claim 19, wherein said disorder is duodenal ulcer, pre-pyloric ulcer, gastric ulcer, oesophageal ulceration, reflux oesophagitis with or without ulceration, bile-reflux gastritis, non ulcer dyspepsia associated with C. pylori gastritis, oesophageal reflux or asymptomatic carrier state.

64 recalled volunteers at 19.3 months
(Average)

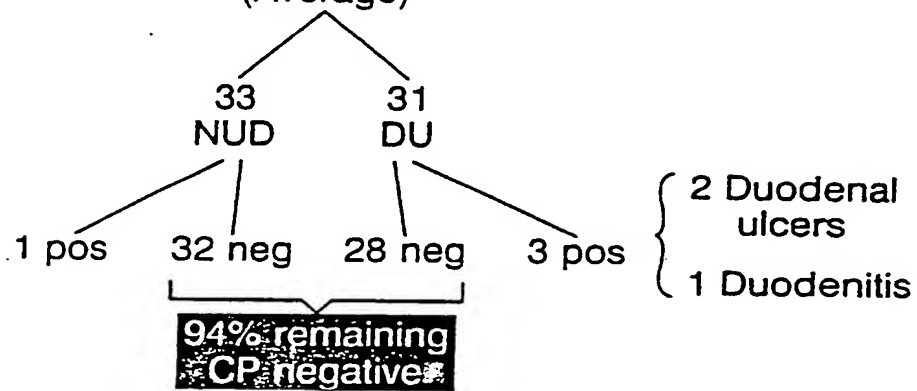
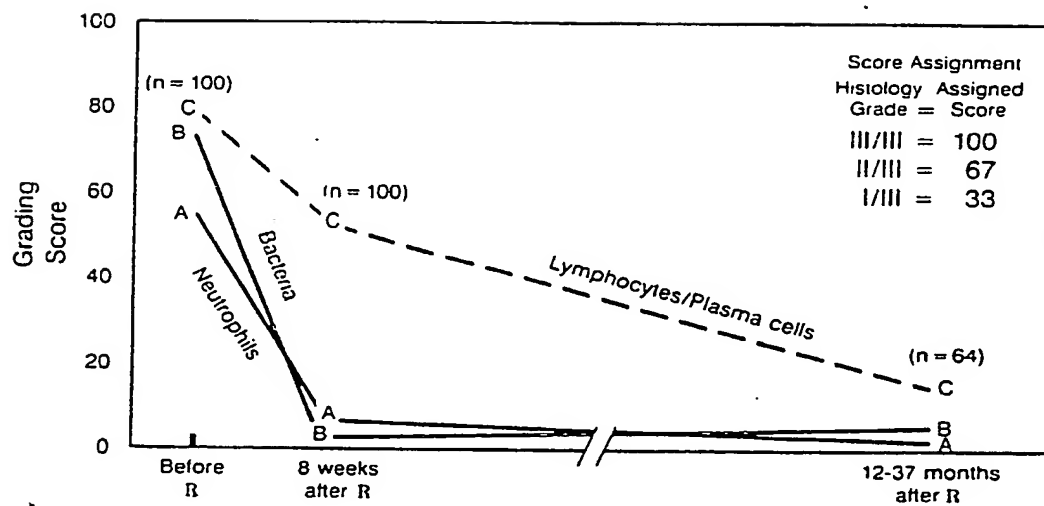


Fig. 2



INTERNATIONAL SEARCH REPORT

International Application No PCT/AU 88/00379

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) *		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int. Cl. ⁴ A61K 33/24, 31/29		
II. FIELDS SEARCHED		
Minimum Documentation Searched *		
Classification System	Classification Symbols	
IPC	A61K 33/00 to 33/44, 27/00, 27/06	
Documentation Searched other than Minimum Documentation to the extent that such documents are included in the fields searched *		
III. DOCUMENTS CONSIDERED TO BE RELEVANT *		
Category *	Citation of Document, ** with indication, where appropriate, of the relevant passages **	Relevant to Claim No. **
X,Y	AU,A, 59026/86 (BORODY) 5 November 1986 (05.11.86), see claim 3	(1,2,8)
Y-	FR,A, 2053002 (PHARKEM S.R.L.) 16 April 1971 (16.04.71)	(1,3,5)
Y	DE,A, 1963496 (Dr Med. HANS VOIGT) 24 June 1971 (24.06.71)	(1)
Y	AU,B, 2014/61 (262452) (WILLESSEN PAPER AND CANVAS) 7 March 1963 (07.03.63)	(1)
Y	Patent Abstracts of Japan, C-475, page 152, JP,A, 62-195329 (NIPPON KAYAKU) 28 August 1987 (28.08.87)	(1,2)
Y	AU,A, 65846/65 (OLIN MATHIESON) 4 May 1967 (04.05.67)	(1-4)
Y	AU,A, 58595/86 (MARSHALL) 18 December 1986 (18.12.86)	(1-6,8)
Y	GB,A, 2054373 (PREBUILT ESTABLISHMENT) 18 February 1981 (18.02.81) see column 1 line 63 to column 2 line 105, claims 5 and 8	(1)
A	EP,A, 206626 (MARSHALL) 30 December 1986 (30.12.86)	
A	EP,A, 206627 (MARSHALL) 30 December 1986 (30.12.86)	(continued)
<p>* Special categories of cited documents: **</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"A" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
28 November 1988 (28.11.88)	01 December 1988 (01.12.88)	
International Searching Authority	Signature of Authorized Officer	
Australian Patent Office	JOHN G. HANSON	

Form PCT/ISA/210 (second sheet) (January 1985)

BEST AVAILABLE COPY

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

A	AU, A, 40841/68 (MASTI-KURE) 22 January 1970 (22.01.70)	
Y	Antimicrobial Agents and Chemotherapy (AMACCQ), Volume 31, No.9, issued September 1987, Van Caekenberghe, Dirk L.; Breysens, Johan; "In vitro Synergistic Activity between Bismuth Subcitrate and Various Antimicrobial Agents against <u>Campylobacter pyloridis</u> (C. pylori)" pages 1429 to 1430	(1-4,6,8)
A	"Martindale. The Extra Pharmacopoeia" 28th Edition, Editor James E.F. Reynolds see pages 927 to 930	

V. ☒ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☒ Claim numbers 19-20 because they relate to subject matter not required to be searched by this Authority, namely:

they are directed to methods for treatment of humans.

2. ☐ Claim numbers _____, because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim numbers _____, because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 8.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON
INTERNATIONAL APPLICATION NO. PCT/AU 88/00379

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Members			
AU 59026/86		WO 8605981		EP 222834	
AU 58595/86		BE 904921 JP 62048623		DE 3619702 ZA 8604449	EP 206625
GB 2054373		CH 638975		JP 56108710	PH 16468
EP 206626		BE 904922 EP 206627		DE 3619733	DE 3619734
EP 206627		BE 904922 EP 206626		DE 3619733 JP 62048624	DE 3619734

END OF ANNEX